REMARKS

Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are pending in the application. Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected. Claims 39 and 42 have been objected to. The indication of the allowable subject matter of Claims 39 and 42 is noted with appreciation. Claims 36, 38, 41, 44, and 47 have been amended. Claims 47-55 have been added. Reconsideration and allowance of Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-55 in view of the above amendments and following remarks is respectfully requested.

Independent Claims 36, 38, 41, and 47

The claimed invention relates to a water-soluble conjugate that includes at least two components: (1) a hydrophilic component that includes a polyalkylene oxide (e.g., PEG); and (2) a hydrophobic component that includes an endosomal membrane disruptive polymer when released from conjugate. The two components covalently linked by a pH-sensitive linkage, the hydrolysis of which releases the hydrophobic component. The water-soluble conjugate is recited in each of independent Claims 36, 38, 41, and 47.

Independent Claims 36, 38, 41, and 47 have been amended to clarify the invention. Each independent claim has been amended to recite that the hydrophobic component of the water-soluble conjugate is an endosomal membrane disruptive carboxylic acid-containing polymer that provides transport through an endosomal membrane when released from the conjugate. Claim 47 has also been amended to conform to independent Claims 36, 38, and 41 to recite that the conjugate is water soluble.

The Rejection of Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 Under 35 U.S.C. §§ 102(b)/103(a)

Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over

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Davaran et al. (Davaran et al., "Hydrophilic Copolymers Prepared From Acrylic Type Derivatives of Ibuprofen Containing Hydrolyzable Thioester Bond," *European Polymer Journal 34*(2):187-192, 1998), as evidenced by the present application, Baroni et al. (Baroni et al., "Effect of Ibuprofen and Warfarin on the Allosteric Properties of Haem-Human Serum Albumin," *European Journal of Biochemistry 268*:6214-6220, 2001), Ito et al. (Ito et al., "Control of Water Permeation by pH and Ionic Strength through a Porous Membrane Having Poly(carboxylic acid) Surface-Grafted" *Macromolecules 25*:7313-7316, 1992), and U.S. Patent No. 6,358,490, issued to Theodore et al. Withdrawal of the rejection is requested for the following reasons.

Claims 36, 38, 41, and 47 are the pending independent claims. Claims 3, 4, 8, 9, 13-15, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

As noted above, independent Claims 36, 38, 41, and 47 have been amended.

Novelty

Applicants submit that the claimed invention is novel in view of the cited reference.

First, each of the independent claims recites a hydrophilic-hydrophobic conjugate that is water soluble. The Office relies on one of the copolymers described in the Davaran reference (MOETE-co-PEGM) as an anticipating hydrophilic-hydrophobic conjugate. However, this copolymer, having a methacrylate backbone with pendant polyethylene glycol (PEG) is not water soluble, but rather "water dispersible." At p. 190, Col. 2, first full paragraph, the reference describes the preparation of "water-dispersible copolymers" (MOETE-co-PEGM) and notes that when "PEGM was used for the copolymer synthesis, spherical water-dispersible polymers were obtained" (see p. 190, Col. 2, second full paragraph, and p. 191, Col. 1, fourth full paragraph). Although the reference describes alternative embodiments that are water-soluble copolymers

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(e.g., MOETE-co-MAAm, MOETE-co-MAAm-co-Vim, and MOETE-co-MA), these copolymers are not hydrophilic-hydrophobic conjugates; they do not include a polyalkylene oxide moiety (e.g., pendant PEG groups). As such, the disclosed alternative embodiments likewise do not anticipate the claimed inventions,

Because neither the Davaran reference nor the other cited references describes a water-soluble conjugate having a hydrophilic component that includes a polyalkylene oxide linked by a pH-sensitive linkage to a hydrophobic component, the references do not describe the claimed inventions and are not anticipatory. Accordingly, withdrawal of the rejection is requested.

Second, applicants submit that the cited references fail to describe the inventions because neither the Davaran reference nor the other cited references describes a conjugate having a hydrophilic polyalkylene-containing component linked by a pH-sensitive linkage to a hydrophobic component that includes an endosomal membrane disruptive carboxylic acid-containing polymer.

As previously set forth in applicants' responses dated May 30, 2008 and February 4, 2009, the Office asserts that the hydrophobic component released by the alleged inherent hydrolysis of the poly(MOETE-co-PEGM) copolymer described in the Davaran reference is poly(methacrylic acid), and further, that the released poly(methacrylic acid) is inherently endosomal membrane disruptive. However, the Office has not provided sufficient technical basis for either of the asserted two inherent features – hydrolysis or endosomal membrane disruption. In particular, the Office has not established that the polyalkylene oxide moieties of the poly(MOETE-co-PEGM) would necessarily be hydrolyzed under the conditions disclosed in the Davaran reference, or under more acidic endosomal physiological pH. Moreover, even if and to the extent such hydrolysis occurs, poly(methacrylic acid) has been evidenced in the record of this application's prosecution as not being disruptive to the endosomal membrane (see Stayton

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Declaration). Because the evidence of record demonstrates that the Davaran reference does not describe a conjugate having a hydrophobic component that is an endosomal membrane disruptive carboxylic acid-containing polymer, the reference is not anticipatory. For this reason, withdrawal of the rejection is respectfully requested.

Non-obviousness

Applicants further submit that the inventions as now claimed are non-obvious in view of the cited references.

KSR Int'l Co. v. Teleflex confirmed that the Graham Factor Analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). 127 S. Ct. 1727, 1739 (2007). The analysis considers (1) the scope and content of the rejected claims; (2) the scope and content of the cited art, (3) the differences between the rejected claims and the cited art, and (4) whether the differences are obvious differences.

As noted above, the inventions as claimed differ from the teaching of the cited references in at least two respects: the references fail to describe a water-soluble conjugate having a hydrophilic component linked by a pH-sensitive linkage to a hydrophobic component that is an endosomal membrane disruptive carboxylic acid-containing polymer.

Applicants submit that the Office has not established *prima facie* obviousness, because (1) there is no apparent reason to modify the teaching of the references to arrive at the claimed inventions, and (2) every element of the invention is not taught or suggested by the art, even if the references were combined, one would not arrive at the claimed invention based on such combination.

The Art of Record Does Not Disclose the Claimed Inventions

As noted, the cited references fail to teach or suggest a water-soluble conjugate having a hydrophilic component comprising polyalkylene oxide linked by a pH-sensitive linkage to a

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hydrophobic component that is an endosomal membrane disruptive carboxylic acid-containing polymer.

Although the Office asserts that the Davaran reference describes a copolymer inherently hydrolyzing to form a copolymer having a poly(methacrylic acid) component, poly(methacrylic acid) is not endosomal membrane disruptive. Evidence demonstrating poly(methacrylic acid)'s lack of ability to disrupt endosomal membranes is of record in this application. Moreover, the poly(MOETE-co-PEGM) copolymer relied upon by the Office is not water-soluble.

Although the Davaran reference describes alternative embodiments that are water-soluble copolymers (e.g., MOETE-co-MAAm, MOETE-co-MAAm-co-Vim, and MOETE-co-MA), these copolymers are not hydrophilic-hydrophobic conjugates; they do not include a polyalkylene oxide moiety (e.g., pendant PEG groups).

No Motivation Exists in the Art to Modify the Davaran Reference in a Manner Arriving at the Inventions

There is no apparent reason to modify the Davaran reference to arrive at the claimed invention.

The Davaran reference discloses polymeric-drug conjugates for delivering ibuprofen to solve the drug's irritant side effects on the gastro-enteric mucosa and its poor water solubility. Because the problem associated with the solubility of the polymeric prodrug has been satisfactorily solved by using certain of the disclosed hydrophilic comonomers and further because monomers such as polymethacrylamide (MAAm), polyvinylimidazole (Vim), and polyethylene glycol methacrylate (PEGM) are well known in the art as a solution for solubilizing hydrophobic drugs or polymers, there is no apparent reason to further modify Davaran's teaching.

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More specifically, there is no apparent reason to select the particular polyalkylene oxide-containing embodiment of the Davaran reference, and no apparent reason to modify such polymer backbone as alleged by the Office for any purpose. In particular, a person of ordinary skill would not have been motivated to combine the various embodiments disclosed within the Davaran reference to arrive at the claimed inventions. Specifically, there is no basis for combining the water-insoluble, polyalkylene oxide-containing embodiment (MOETE-co-PEGM), with any of the water-soluble, polyalkylene oxide-lacking embodiments (MOETE-co-MAAm, MOETE-co-MAAm-co-Vim, and MOETE-co-MA). There is likewise no basis for selecting or modifying the water-soluble methacrylic acid-containing embodiments (MOETE-co-MA) to arrive at the inventions. There is no explicit suggestion or teaching within the Davaran reference or other references of record for such combinations. Significantly, the data disclosed in the Davaran reference would have led one away from such combinations, and would have led one away from features significant for the presently-claimed inventions. The polyalkylene oxide-containing embodiment (MOETE-co-PEGM) performed less satisfactory than methacrylamide embodiments (MOETE-co-MAAm; MOETE-co-MAAm-co-Vim) with respect to rate and extent of ibuprofen hydrolysis. The methacrylic acid-containing embodiments (MOETE-co-MA) were the worst performing embodiments with respect to rate and extent of ibuprofen hydrolysis (See generally, p. 191 (Figs. 1, 2, 3) and p. 191, Col. 1, Paragraph 4):

- poly(MOETE-co-MAAm-co-Vim) (Fig. 3) – 80% ibuprofen hydrolysis w/in 30 hours
- poly(MOETE-co-MAAm) (Fig. 2) – 50% ibuprofen hydrolysis w/in 30 hours
- poly(MOETE-co-PEGM) (p. 191, Col. 1, Paragraph 4) between 37% and 50% ibuprofen hydrolysis w/in 30 hours
- poly(MOETE) (Fig. 1) – 37% ibuprofen hydrolysis w/in 30 hours
- poly(MOETE-co-MAA) (Fig. 2) – 30% ibuprofen hydrolysis w/in 30 hours

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The Office has not articulated any reason as to why a person of ordinary skill would have selected the poly(MOETE-co-PEGM) embodiment, or would have modified such embodiment in a manner that would have lead to the claimed inventions.

Hence, the Davaran reference does not disclose, teach, or suggest the inventions as presently claimed, and a person of skill in the art would not have been led to such inventions based on the teaching of the reference. As discussed further below, the other art of record likewise does not provide any basis to select, or even if selected, to modify the polyalkylene-oxide containing embodiment (MOETE-co-PEGM) as disclosed in the Davaran reference in a manner that would have led to the as-claimed inventions.

An Inherent Feature Cannot be Relied Upon to Establish Obviousness

The Office's *prima facie* case of obviousness appears to be impermissibly premised on inherency. As noted above, the Examiner alleges first an inherent hydrolysis of the ester bond of poly(MOETE-co-PEGM) to provide poly(methacrylic acid), and second, an inherent activity for endosomal membrane disruption of the resulting poly(methacrylic acid). However, the law is clear that an Examiner cannot rely on an inherent feature to establish obviousness.

The Office's reliance on the alleged inherent membrane disruptive feature is misplaced in the context of an obvious determination. Courts have long held that inherency and obviousness are entirely different questions. "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Shetty*, 195 USPQ 753 (CCPA 1977) quoting *In re Spormann* 150 USPQ 449 (CCPA 1966). *See* also *In re Rijckaer*, 28 USPQ2d 1955 (Fed. Cir. 1993) (retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection). In the instant application, even if one assumes, *arguendo,* that poly(MOETE-co-PEGM) becomes hydrolyzed to poly(MOETE-co-MA), and even if one assumes, *arguendo,* that such methacrylic acid-containing polymer has

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endosomal membrane disrupting activity – a contention not supported by the record – it is improper for the Office to rely on either of such features to establish obviousness. Because the required hydrolysis and endosomal membrane disrupting activity are at most inherent features, a person of ordinary skill in the art would not have necessarily understood or been motivated with respect to a beneficial effect of such features or the significance of applying such features in the context of the present invention. As such, these inherent features cannot form the basis for rejecting the claims as obvious. *See In re Naylor,* 152 USPQ 106 (CCPA 1966).

The Office Appears to Rely on Impermissible Hindsight

Because the Office has not established motivation existing in the art of record, but rather appears to be using the teaching of the instant specification as a basis for selecting various features to apply in combination to arrive at the claimed invention, the outstanding rejections appear to be based on improper hindsight. To imbue the skilled person with the knowledge of the claimed invention, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the hindsight analysis where that which only the inventor taught is used against its teacher (see *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). The Supreme Court in KSR cautioned against hindsight bias distortion in assessing obviousness. KSR, 127 S. Ct. at 1742.

For the foregoing reasons, the claimed inventions are non-obvious in view of the cited references. Withdrawal of the rejection is requested.

The Rejection of Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47

Under 35 U.S.C. § 103(a)

Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of the Davaran reference in view of U.S. Patent No. 4,571,400, issued to Arnold, and Vinogradov et al. (Vinogradov et al.,

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"Self-Assembly of Polyamine-Poly(ethylene glycol) Copolymers with Phosphorthioate Oligonucleotides," *Bioconjugate Chemistry* 9(6):805-812, 199), as evidenced by the present application, the Baroni reference, the Ito reference, and the Theodore reference. Withdrawal of the rejection is requested for the following reasons.

Claims 3, 4, 8, 9, 13-17, 19, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

The Vinogradov reference teaches cationic copolymer for DNA delivery by conjugating poly(ethylene glycol) (PEG) and polyamines: polyspermine (PSP) and polyethylenimine (PEI). The cationic copolymers include the conjugates of polyethylene glycol (PEG) and polyamines. The PEG and the polyamines are linked through a carbamate linker, i.e., -NH-COO-. The cationic copolymers are complexed to antisense oligonucleotides (PS-ODNS).

The Arnold reference is directed to pharmaceutical compositions containing dihydrocodeine or a pharmaceutically acceptable acid addition salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof that are useful in treating pain. The reference discloses a wide range of pharmaceutically acceptable carriers for use with ibuprofen.

Because neither the Vinogradov reference nor the Arnold reference discloses a conjugate having a hydrophilic component linked by a pH-sensitive linkage to a hydrophobic component that is an endosomal membrane disruptive carboxylic acid-containing polymer, as in the claimed invention, the deficiencies of the teachings of the Davaran, Baroni, Ito, and Theodore references noted above with regard to independent Claims 36, 38, 41, and 47 are not cured by the teachings of the Vinogradov and Arnold references.

Because the cited references fail to teach, suggest, provide any motivation, or otherwise render obvious the invention as now claimed, the claimed invention is not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

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New Claims 48-55

Claims 48-55 have been added. Claims 48-55 depend from Claim 36. Support for the new dependent claims can be found throughout the specification as originally filed. Support for Claim 48 can be found at page 11, lines 26-28. Support for Claim 49 can be found at page 12, lines 11-12. Support for Claim 50 can be found at page 12, lines 9-10 and page 35, Example 2. Support for Claim 51 can be found at page 12, lines 3-10. Support for Claim 52 can be found at page 11, line 26-page 12, line 16. Support for Claims 53 and 54 can be found at page 26, line 10. Support for Claim 55 can be found at page 26, line 15.

Conclusion

In view of above amendments and foregoing remarks, applicants believe that Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-55 are in condition for allowance. If any issue remains that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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